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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,910	07/15/2003	Yoshihiko Nishimura	81918.0003	7180

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,910	NISHIMURA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22 and 24-35* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☒ Claim(s) *35* is/are allowed.

6)☒ Claim(s) *15-17,19,22 and 24-34* is/are rejected.

7)☒ Claim(s) *18 and 20-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Status of the Claims

1. Claims 12-22 and 24-35 are pending.

Applicants' amendment filed on April 28, 2005 is acknowledged. Applicants' response has been fully considered. Claims 12 and 15 have been amended, claim 23 has been cancelled, and new claims 25-35 have been added. This application contains claims 12-14 as amended drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Thus, claims 15-22 and 24-35 are examined.

Objection Withdrawn

2. The previous objection to claims 12-14 is withdrawn, and the status of claims 12-14 is acknowledged in view of applicant's amendment to the claims in the amendment filed April 28, 2005.

Withdrawn Claim Rejections - 35 USC § 102

3. The previous rejection of claims 12-17, 19, 22 and 24 under 35 U.S.C. 102(b) as anticipated by Oppermann *et al.* (WO89/09788), is withdrawn in view of applicant's amendment to the claim, and applicant's response at pages 8-12 of the amendment filed April 28, 2005.

4. The previous rejection of claims 12-22 and 24 under 35 U.S.C. 102(e) as anticipated by Rueger *et al.* (U.S. Patent 6,281,195), is withdrawn in view of applicant's amendment to the

claim, and applicant's response at pages 8-12 of the amendment filed April 28, 2005.

New Claim Objection

5. Claim 15 is objected to because of the use of the terms "the peptide N-terminal is acetylated" and "the peptide C-terminal is amidated". Use of the terms "the peptide is N-terminally acetylated" and "the peptide is C-terminally amidated" is suggested.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 25-27, 29, 32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Oppermann *et al.* (WO89/09788).

Oppermann *et al.* teach a synthetic osteogenic protein comprising an amino acid sequence of OP1 peptide (102 amino acid residues), which contains the amino acid sequence of

SEQ ID NO:11 at residues 57-76, and can induce endochondral bone formation and bone marrow differentiation at the locus of the implant, when properly folded and implanted in a mammal in association with a matrix (pages 6 and 8; claims 25, 26 and 32); and the matrix is a biocompatible and biodegradable material such as demineralized xenogenic bone, collagen, homopolymers and copolymers of glycolic acid and lactic acid, hydroxypatite, tricalcium phosphate and other calcium phosphate (page 14, second paragraph-page 15, first paragraph; claim 27). The osteogenic protein can be prepared as active protein at pH 8 using Tris buffer containing Guanidine•HCl and dithiothreitol (page 30, second paragraph-page 31, first paragraph; claims 29 and 34). The term "consisting essentially of" reads as "comprising", since the osteogenic protein containing OP1 in the reference has the same osteogenetic activity as the claimed peptide.

7. Claims 25-32 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Rueger *et al.* (U.S. Patent 6,281,195, priority date Feb. 7, 1997).

Rueger *et al.* teach an osteogenic protein such as OP1 (431 residues; SEQ ID NO:2 of the patent; column 12, line 4), which contains the amino acid sequence of SEQ ID NO:11 at residues 386-405, and can induce endochondral bone formation sufficient to repair critical-sized, segmental bone defects, when admixed with a biocompatible, amorphous non-rigid carrier as a matrix-free device, where the carrier can be alkylcelluloses, poloxamers, dextrins, sugars, lactose, mannitol, and physiological saline (PBS) (column 3, lines 30-67; column 10, line 42-column 11, line 11; column 16, line 40-column 17, line 11; claims 25-27, 29, 30, 32 and 34). The osteogenic devices were made with 62.5 μg lyophilized OP-1 with 25 mg collagen matrix (0.0625 mg/25 mg = 0.25%; column 20, lines 11-60; claim 28), and the osteogenic devices in

solution were prepared with a desired dose of OP-1 (5-25 mg) in 20 mM acetate buffer in a 100 µl injection volume (e.g., 5 mg/100 µl = 5 g/100 ml = 5%; column 21, lines 24-33; claim 31). The term "consisting essentially of" reads as "comprising", since the osteogenic protein containing OP1 in the reference has the same osteogenetic activity as the claimed peptide.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Previous rejection of claims 15-17, 19, 22 and 24 under 35 U.S.C. 103(a) as being unpatentable over Oppermann *et al.* (WO89/09788) in view of Lipton (U.S. Patent 5,028,592) is maintained, and claims 25-27, 29 and 32-34 have been added. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Oppermann *et al.* teach a synthetic osteogenic protein comprising an amino acid sequence of OP1 (102 amino acid residues), which contains the amino acid sequence of SEQ ID NO:11 at residues 57-76, and can induce endochondral bone formation and bone marrow differentiation at the locus of the implant, when properly folded and implanted in a mammal in association with a matrix (pages 6 and 8; claims 15, 16, 22, 25, 26 and 32); and the matrix is a biocompatible and biodegradable material such as demineralized xenogenic bone, collagen, homopolymers and copolymers of glycolic acid and lactic acid, hydroxypatite, tricalcium phosphate and other calcium phosphate (page 14, second paragraph-page 15, first paragraph; claims 17 and 27). The osteogenic protein can be prepared as active protein at pH 8 using Tris

buffer containing Guanidine•HCl and dithiothreitol (page 30, second paragraph-page 31, first paragraph; claims 19, 24, 29 and 34). However, Oppermann *et al.* do not disclose the peptide having N-terminal acetylated or C-terminal amidated.

Lipton teaches a bioactive peptide is protected by an acetyl group at N-terminus or an amido group at C-terminus, and indicates the protected peptide is more active pharmacologically than the unprotected peptide because the protected peptide is less susceptible to acid hydrolysis or enzymatic attack and degradation (column 4, lines 56-66).

At the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to use the osteogenic peptide comprising SEQ ID NO:11 taught by Oppermann *et al.* to prepare the protected peptide by amidation at C-terminal or acetylation at N-terminal as taught by Lipton (claim 33) because the peptide with N- or C-terminal protected would reduce its susceptibility to acid hydrolysis or enzymatic attack and degradation, and is more active pharmacologically than the unprotected peptide. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Response to Arguments

Applicants indicate that there is no motivation or suggestion to combine the teaching of Oppermann with the teaching of Lipton in the manner suggested by the Office. Furthermore, if the teaching of Oppermann were to be combined with the teaching of Lipton, the principle of operation of Oppermann would be destroyed. Oppermann teaches a synthetic osteogenic protein comprising an amino add sequence of OPI (102 amino acids), which contains the amino acid sequence of SEQ ID NO:11 at residues 57-76. An acetylation at the N-terminal end (residue 57)

of SEQ ID NO:11 or an amidation at the C-terminal end (residue 76) of SEQ ID NO:11 would shorten the OP1 102 amino acid sequence. Consequently, the synthetic osteogenic protein taught by Oppermann would no longer exist. Moreover, MPEP 2143.01 states "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified then the teachings of the references are not sufficient to render the claims prima facie obvious." (pages 9-11 of the response).

Applicants' response has been fully considered, however, the argument is found persuasive because Lipton teaches a bioactive peptide with N- or C-terminal protected would reduce its susceptibility to acid hydrolysis or enzymatic attack and degradation, and is more active pharmacologically than the unprotected peptide, which is the motivation to acetylate the N-terminal end or to amidate the C-terminal end of an osteogenic peptide. Furthermore, the acetylation at the N-terminus or amidation at the C-terminus of the osteogenic peptide, which contains SEQ ID NO:11, would not shorten the OP1 (102 amino acid) sequence or change the principle of operation of the prior art invention since the modification occurs at the N-terminus or C-terminus of OP1, not the N-terminus or C-terminus of the amino acid sequence of SEQ ID NO:11. Therefore, the combination of two references was prima facie obvious to result in the claimed invention.

Claim Objection

9. Claims 18 and 20-21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

10. Claims 15-17, 19, 22 and 24-34 are rejected; claims 18 and 20-21 are objected to; and claim 35 is free of art and allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
June 29, 2005

KATHLEEN KERR, PH.D.
PRIMARY EXAMINER
SPE